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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DAVID FARROW

Appeal 2010-002895
Application 10/601,378
Technology Center 1600

Before ERIC GRIMES, LORA M. GREEN, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 involving claims to methods of detecting analyte particles in a fluid. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

Statement of the Case

The Claims

Claims 1-5, 7, 8, and 22-29 are on appeal. Claim 1 is representative. Claim 1 reads as follows:

> 1. A method for detecting the presence of an analyte particle in a fluid, said method comprising, sequentially:
>
> filtering a sample of said fluid from a first chamber to a second chamber through a filter sized to pass said analyte particle and particles smaller than said analyte particle, retaining in said first chamber particles in said sample larger than said analyte particle thereby forming in said second chamber a filtered sample;
>
> adding to said filtered sample in said second chamber a reagent that specifically interacts with said analyte particle to form a reagent-analyte particle complex that is larger than said analyte particle;
>
> filtering said filtered sample from said second chamber through a filter sized to pass particles that are smaller than said reagent-analyte particle complex thereby forming in said second chamber a further filtered sample;
>
> testing said further filtered sample in said second chamber for the presence of residual particles, wherein the presence of said residual particles identifies the presence of said reagent-analyte particle complex in said second chamber, and wherein the presence of said-analyte particle complex is indicative of the presence of said analyte particle in said fluid and wherein the absence of said reagent-analyte particle complex in said second chamber is indicative of the absence of said analyte particle in said fluid.

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Piesold et al.	WO 01/85341 A1	Nov. 15, 2001
Petersen et al.	US 2002/0042125 A1	Apr. 11, 2002
Bernhardt et al.	US 6,391,657 B1	May 21, 2002
Chou et al.	US 2004/0072278 A1	Apr. 15, 2004

Tullis et al., *HIV affinity hemodialysis as a treatment for AIDS*, AM. CLINICAL LABORATORY 22-23 (2001).

The issues

A. The Examiner rejected claims 1-5, 7, 8, and 22-29 under 35 U.S.C. § 103(a) as obvious over Tullis, Bernhardt, Petersen and Piesold (Ans. 3-7).

B. The Examiner rejected claims 1-5, 7, 8, and 22-29 under 35 U.S.C. § 103(a) as obvious over Chou, Bernhardt, and Piesold (Ans. 7-11).

A. 35 U.S.C. § 103(a) over Tullis, Bernhardt, Petersen, and Piesold

The Examiner finds it "obvious to modify the filter of Tullis et al. using the CD4 reagent of Bernhardt et al. with the microfluidics device of Piesold because Piesold shows the device provides a beneficial enhancement in the feasibility of miniaturizing experiments and assays" (Ans. 6).

Appellant contends that "none of the cited references provide the step of testing for the presence of residual particles within the chamber in which a reagent-analyte particle complex is formed" (App. Br. 8). Appellant contends that:

> In order to relate Piesold to the invention as claimed in present claim 1 as the Examiner has done would require modification of the device in Piesold in such a manner as to destroy the purpose or function of the Piesold device, i.e. to

> reverse the flow backwards through the device in Piesold, destroying the function of filter 4 for trapping particle beads 6 within reaction chamber 10 (since there would be nothing stopping the beads from flowing out inlet 2).

(App. Br. 17). Appellant contends that the "four references in combination do not disclose, describe or suggest testing for the presence of a residual particles within a chamber of the device in which a reagent-analyte particle complex is formed" (App. Br. 17).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Tullis, Bernhardt, Petersen, and Piesold render claim 1 obvious?

Findings of Fact

1. Tullis teaches that "[b]lood from the patient is pumped through the hollow fibers, each of which has multiple submicron-sized pores to allow passage of the virus and simultaneously prevent preformed blood elements from exiting the fiber" (Tullis 22, col. 1-2).

2. Tullis teaches that "[d]uring transit, the virus is transported by a combination of diffusion and convection through the pores and into the extra fiber space which is filled with a matrix comprising antiviral antibodies covalently coupled to a beaded agarose or silica solid support" (Tullis 22, col. 2).

3. Tullis teaches that the "concentration of HIV was measured by real-time PCR and confirmed by p24 enzyme linked immunosorbent assay (ELISA) both directly in virus concentrated from plasma and RNA extracts from virus trapped on the column" (Tullis 23, col. 1).

4. Bernhardt teaches "the removal of viruses from aqueous solutions, as a rule protein solutions, by ultrafiltration" (Bernhardt, col. 1, ll. 4-5). Bernhardt teaches that in "the most general form, the present invention makes it possible to increase the size of any constituents of an aqueous solution by binding to high molecular weight ligands to such an extent that separation is then possible from the now smaller constituents in a filtration step" (Bernhardt, col. 2, ll. 25-29).

5. Bernhardt teaches that the "viruses to be removed are increased in size by binding to high molecular weight ligands, preferably specific antibodies . . . to such an extent that they can be held back by filtration" (Bernhardt, col. 2, ll. 11-18).

6. Bernhardt teaches that CD4 is a ligand which can be used to bind and retain HIV (*see* Bernhardt, col. 2, ll. 30-50).

7. Figure 2 of Piesold is reproduced below:

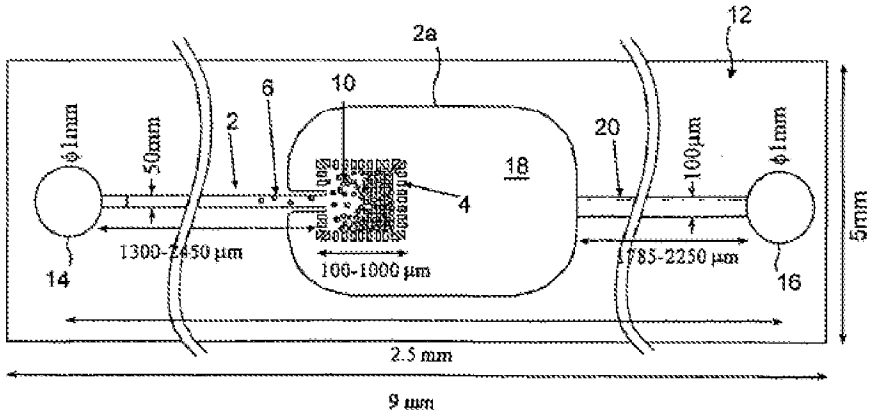

FIG. 2

"Figure 2 shows schematically a plan view of an embodiment of an apparatus" (Piesold 6, l. 3).

8. Piesold teaches "a reaction apparatus comprising a porous reaction chamber for trapping one or more particles therein and a reaction

monitoring means arranged to monitor the particles trapped in the reaction chamber; wherein the reaction chamber is arranged so as substantially to correspond in shape to the reaction monitoring means" (Piesold 3, ll. 25-28).

9. Piesold teaches that while "preferred applications of the invention are for reactions in which an analyte is immobilised on a bead of some sort, it will be appreciated that apparatus in accordance with the invention may also be used in applications not involving beads – e.g. cell-cell separations, cell deformability tests and particle filtration" (Piesold 2, l. 31 to 3, l. 3).

10. Piesold teaches a DNA sequencing method in which "[b]iotinylated inner PCR product was immobilized onto the streptavidin coated beads" (Piesold 13, ll. 11-12).

11. Piesold teaches that "[s]ince the sample flow-through does not displace the beads or their surface functional groups multi-step reactions can be implemented at one location in the microfabricated device, facilitating optical detection" (Piesold 12, ll. 22-25).

12. The Examiner finds that "Peterson et al. show an injection molded plastic filtration device . . . Peterson et al. teach the device has a solid support for capturing a desired analyte" (Ans. 6).

Principles of Law

The Examiner has the initial burden of establishing a prima facie case obviousness under 35 U.S.C. § 103. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning

with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Analysis

While some of the elements of Claim 1 are individually found in the cited prior art references, the Examiner has not clearly demonstrated that the references disclose multiple filtration steps in which a sample is filtered and then the filtrate is further filtered to remove components. Also the Examiner has not provided a reason to combine these scattered teachings in the manner claimed by Appellant. That is, the Examiner relies on the PCR and ELISA testing by Tullis to satisfy the step in Claim 1 of "testing said further filtered sample in said second chamber", but these tests are not performed in the second chamber, but rather are performed on material which is removed from the column and would not be in the chamber (FF 1-3). Bernhardt has no interest in testing for viruses, but rather is interested in removing viruses from solutions using the capture moieties (FF 4-6). Petersen was not relied upon for this element (FF 12).

While Piesold does teach detection of material in a chamber in the context of a DNA sequencing method (FF 10-11), Piesold also does not suggest trapping the analyte with a specific reagent in the second chamber (FF 10). In Piesold's DNA sequencing example, the analyte is the bead bound single stranded PCR amplified DNA after annealing to a primer, and no capture occurs in the chamber (FF 10).

We therefore agree with Appellant that "there is no reason that a skilled person would be motivated to combine Tullis, Bernhardt, Petersen and Piesold to arrive at the present method of claim 1" (App. Br. 18).

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that Tullis, Bernhardt, Petersen, and Piesold render claim 1 obvious.

B. 35 U.S.C. § 103(a) over Chou, Bernhardt, and Piesold

The Examiner finds:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the differential microfluidics particle filtering system of Chou et al. with the formation of CD4-HIV complexes for the purpose of increasing the HIV particle size of Bernhardt et al. because Bernhardt et al. show that by forming a reagent-particle complex increased filtration rates can be obtained. It would have been further obvious to use CD4 as the HIV complex-forming reagent because Chou et al. teach that CD4 is the primary receptor for HIV. It would also have been further obvious to modify the filtration device of Bernhardt et al. with the microfluidics system of Chou et al. because Chou et al. teach the microfluidics system has the advantages of improved speed, accuracy, safety, and cost. It would have been further obvious to modify the microfluidics filtering system of Chou et al. using the CD4 reagent of Bernhardt et al. with the microfluidics device of Piesold because Piesold shows the device provides a beneficial enhancement in the feasibility of miniaturizing experiments and assays. It would have been further obvious to modify the microfluidics filtering system of Chou et al. using the CD4 reagent of Bernhardt et al. with the microfluidics device design of Piesold because the application of differential filtering was known in the art at the time of invention as demonstrated by Bernhardt et al. One of ordinary skill in the art would have been capable of applying differential filtering to the device

> of Piesold that was ready for improvement and the results would have predictable to one of ordinary skill the art.

(Ans. 10-11).

Appellant contends that "Chou and Bernhardt together in view of Piesold reveals that the new three-reference combination does not disclose, describe or suggest testing for the presence of residual particles within the chamber in which a reagent-analyte particle complex is formed, as claimed in currently pending claim 1" (App. Br. 23). Appellant contends that the filtering arrangement of Chou

> does not suggest or provide an intervening step that involves making the apparent size of the analyte larger based on a specific interaction following a first filtration step, a subsequent second filtration step and then testing for the presence of residue remaining within the chamber in which a reagent-analyte complex is formed, as required by present claim 1.

(App. Br. 25). Appellant contends that "Piesold does not mention addition of reagent, formation of a reagent-analyte complex, filtration of particles smaller than the complex and testing for the presence of a residue within the chamber in which the complex is formed, as required by pending claim 1" (App. Br. 26).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Chou, Bernhardt, and Piesold render claim 1 obvious?

Findings of Fact

13. Chou teaches that "[v]iruses may be manipulated and/or analyzed as particles in microfluidic systems . . . Exemplary viruses may include HIV" (Chou 8 ¶ 0167).

14. Chou teaches "size-selective channels may retain particles that are too large to enter the channels. (Size-selective channels also may be referred to as filter channels, micro channels, or particle-restrictive or particle-selective channels.)" (Chou 11 ¶ 0214).

15. Chou teaches that

> input particles may have a common size, such as cells from a homogeneous cell population, or they may have a range of sizes, such as cells from blood. In some embodiments, the diameter of filter channel 616 allows size-selective retention of a single particle. For example, the diameter may be large enough to receive certain particles in a heterogeneous particle population, such as red blood cells, but small enough to exclude others, such as white blood cells.

(Chou 30 ¶ 0461).

16. Chou teaches that "[c]ell combs also can be cascaded so that objects of different sizes are filtered out at different stages" (Chou 31 ¶ 0468).

17. Chou teaches "microfluidic systems for sorting and analyzing heterogeneous populations of particles, particularly cells, based on differences in particle size" (Chou 47 ¶ 0655).

18. Chou teaches that "the system may be modified to include a serial set of retention mechanisms . . . Each successive mechanism may have a reduced diameter of channel . . . With this arrangement, larger particles are

retained earlier in the series of mechanisms, whereas smaller particles are retained later in the series" (Chou 47 ¶ 0660).

19. Chou teaches that "[p]articles retained in the retention mechanism . . . may be treated and analyzed. Particles may be treated by exposing them to desired reagents . . . Systems . . . may enable on-chip staining and washing, eliminating any need for multiple pipeting and/or centrifugation steps" (Chou 47 ¶ 0661).

20. Chou teaches that "characteristics of particles may be detected or otherwise detected while the particles are relatively stationary, such as when localized in chamber" (Chou 47 ¶ 0662).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417. Moreover, an "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982). As noted by the Court in *KSR*, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR* at 421.

Analysis

Claim 1

Chou teaches detection of analyte particles in fluids (FF 13). Chou teaches "to include a serial set of retention mechanisms . . . Each successive mechanism may have a reduced diameter of channel . . . With this

arrangement, larger particles are retained earlier in the series of mechanisms, whereas smaller particles are retained later in the series" (Chou 47 ¶ 0660; FF 18). Thus, Chou teaches a series of chambers in which the sample is filtered to retain large particles in the first chamber and forming the filtered sample in a second chamber, which is then itself filtered and larger particles are retained in the second chamber and smaller particles flow further through the device (FF 16-18). Chou teaches that "[c]ell combs also can be cascaded so that objects of different sizes are filtered out at different stages" (Chou 31 ¶ 0468; FF 16).

Chou teaches that "characteristics of particles may be detected or otherwise detected while the particles are relatively stationary, such as when localized in chamber" (Chou 47 ¶ 0662; FF 20).

The Examiner acknowledges that Chou does not "show the formation of a reagent-particle complex that is separated from particles smaller than the complex" (Ans. 8). However, the Examiner relies on Bernhardt to teach that the "viruses to be removed are increased in size by binding to high molecular weight ligands, preferably specific antibodies . . . to such an extent that they can be held back by filtration" (Bernhardt, col. 2, ll. 11-18; FF 5).

We agree with the Examiner that "Bernhardt et al. show the formation of analytes reagent complexed that are larger than a selected pore size, and Chou et al. and Bernhardt et al. show embodiments directed to the analysis of blood for particular analyte particles" (Ans. 15).

Appellant contends that "Chou and Bernhardt together in view of Piesold reveals that the new three-reference combination does not disclose,

describe or suggest testing for the presence of residual particles within the chamber in which a reagent-analyte particle complex is formed, as claimed in currently pending claim 1" (App. Br. 23).

We are not persuaded. Chou is expressly interested in separating virus particles into a "residual" chamber for detection after size separation and Chou teaches detecting these particles (FF 13-20). Bernhardt teaches a method of retaining virus particles into a particular chamber by adding a component to increase the size of the particles (FF 4-6). Consistent with *KSR*, the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR* at 416. Here, Bernhardt teaches that in "the most general form, the present invention makes it possible to increase the size of any constituents of an aqueous solution by binding to high molecular weight ligands to such an extent that separation is then possible from the now smaller constituents in a filtration step" (Bernhardt, col. 2, ll. 25-29;FF 4).

We conclude that an ordinary practitioner, motivated by Chou to retain some particles while excluding others (FF 14-16) would have reasonably applied the method of Bernhardt to permit separation of particles (FF 4-6).

> Appellant contends that the filtering arrangement of Chou does not suggest or provide an intervening step that involves making the apparent size of the analyte <u>larger</u> based on a <u>specific interaction</u> following a first filtration step, a subsequent second filtration step and then <u>testing for the presence of residue remaining within the chamber in which a reagent-analyte complex is formed</u>, as required by present claim 1.

(App. Br. 25). Appellant contends that "Piesold does not mention addition of reagent, formation of a reagent-analyte complex, filtration of particles smaller than the complex and testing for the presence of a residue within the chamber in which the complex is formed, as required by pending claim 1" (App. Br. 26).

We are not persuaded. Both of these arguments do not address the combined teachings of the prior art, but rather, separately argue the references. However, the Examiner is relying upon the combination of references, since "[o]ften, it will be necessary . . . to look to interrelated teachings of multiple [references] . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Here, we agree with the Examiner that the interrelated teachings of Chou, Bernhardt, and Piesold together render claim 1 obvious, since Bernhardt teaches the concept of adding a retention component and Chou teaches size selection of particles into multiple chambers (FF 4-6, 13-18).

Claims 22 and 26

Appellant relies upon overcoming the base rejection for claims 22 and 26, but also argues that "there is no reason or motivation to combine and modify the cited references in order to arrive at a detection method for detecting the presence of human immundodeficiency virus in a fluid as claimed in present claim 22" (App. Br. 30). Appellant similarly argues that claim 26 incorporates HIV detection (*see* App. Br. 31).

We are not persuaded. Chou teaches that "[v]iruses may be manipulated and/or analyzed as particles in microfluidic systems . . . Exemplary viruses may include HIV" (Chou 8 ¶ 0167; FF 13). Thus, Chou expressly teaches detection of HIV (FF 13) and Bernhardt teaches retention of HIV using CD4 (FF 6).

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Chou, Bernhardt, and Piesold render claim 1 obvious.

SUMMARY

In summary, we reverse the rejection of claims 1-5, 7, 8, and 22-29 under 35 U.S.C. § 103(a) as obvious over Tullis, Bernhardt, Petersen and Piesold.

We affirm the rejection of claims 1, 22, and 26 under 35 U.S.C. § 103(a) as obvious over Chou, Bernhardt, and Piesold. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 2-5, 7, 8, 23-25, and 27-29 as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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